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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/903,943	07/11/2001	Avi Ashkenazi	10466/88	1367

35489 7590 05/06/2003

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EXAMINER
KAUFMAN, CLAIRE M

ART UNIT	PAPER NUMBER
1646	16

DATE MAILED: 05/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/903,943	ASHKENAZI ET AL
Examiner	**Art Unit**
Claire M. Kaufman	1646

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s) _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The amendment filed 2/19/03 has been entered.

Response to Arguments

The rejection of claims 39, 44 and dependent claims under 35 USC 112, second paragraph, is withdrawn in view of the amendment to the claims which resolved the problem of use of two different terms. As used in the claims, the term "specifically binds" in itself is not indefinite.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment

The declaration under 37 CFR 1.132 filed February 19, 2003, is insufficient to overcome the rejection of claims 39-44 based upon 35 USC 101 and 112, first paragraph, as set forth in the last Office action because: While the declaration and accompanying references show that "real-time PCR" is a reliable means of determining gene copy number in cells or tissues, there are utility and enablement issues of aneuploidy and antibody *vs.* DNA not resolved by the declaration that require the rejection to be maintained. The utility and enablement for claims 39-44 are further discussed under the appropriate section for the rejections below.

Claim Rejections - 35 USC § 101

Claims 39-44 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office action (paper #11) on pages 3-4.

Applicants argue the gene amplification data in the present application are sufficient to establish utility of antibodies to the PRO339 polypeptide because such amplification is "an essential mechanism for oncogene activation" and occurs in most solid tumors and PRO339 showed 2 to 3 fold gene amplification in some lung and colon tumors. The argument has been fully considered, but is not persuasive. Even though in some circumstances and as discussed in the declaration, TaqMan™ real-time PCR can accurately and reproducibly assess gene amplification, in cancerous tissues it is necessary to account for the possibility of aneuploidy.

This was discussed in the previous Office action on page 4, lines 17-21. Sen et al. (Curr. Opin. Oncol., 2000, previously cited) begin by saying "Numeric aberrations in chromosomes, referred to as aneuploidy, is commonly observed in human cancer." Therefore, because the gene amplification observed for PRO339 is small and could reasonably be expected to be due to aneuploidy, the implicit utility of a lung or colon tumor diagnostic is not specific and substantial.

Applicants argue that the number and type of normal tissues used as controls was stated in the specification. The Examiner thanks Applicants for pointing out the data for the normal control, which is the genomic DNA from 10 normal healthy individuals.

Applicants argue that even though the DNA has been shown to be amplified, the antibody claimed has utility even though follow-up tests might be necessary, for example, to develop the antibody or encoded protein into a diagnostic product. The argument has been fully considered, but is not persuasive. Assuming the DNA had utility as a lung and colon tumor marker, which it does not as discussed in the previous Office action and above, the encoded protein and its cognate antibody would not have utility because it is not known what the protein does or if the level protein in tumors corresponds to nucleic acid transcript level, *i.e.*, if an increased gene amplification in lung and colon tumors corresponds to an increased amount of expressed protein. It does not necessary follow that an increase in gene copy number results in increased gene expression and increased protein expression, such that antibodies would be useful in diagnostically or as a target for cancer drug development. For example, Pennica et al. (1998, PNAS USA 95, p.14722, second paragraph; Exhibit D of the declaration) teaches that:

> An analysis of WISP-1 gene amplification and expression in human coon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISP-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient.

Additionally, Hayes et al. (Electrophoresis 19 :1862-1871, 1998) studied 80 proteins relatively homogenous in half-life and expression level, and found no strong correlation between protein and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. It was concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and

Figure 1). Therefore, because it cannot be concluded that the PRO339 is useful as a diagnostic marker for colon or lung cancer, neither the protein nor antibody that specifically binds it has utility. Significant further research would be required to find out what the protein does and if and how it is linked to lung and/or colon cancer. For the reasons discussed above, the asserted utility for the claimed antibody as a diagnostic marker for identifying lung or colon cancer is not specific and substantial.

Claim Rejections - 35 USC § 112, First Paragraph

Claims 39-44 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants argue that a substantial, specific and credible utility for antibodies that bind PRO339 polypeptide has been shown as discussed for the preceding 35 USC 101 rejection, so that it would not require undue experimentation to use the claimed invention. The argument has been fully considered, but is not persuasive. For reasons set forth in the previous Office action and as discussed addressing the 1.132 declaration and rejection under 35 USC 101 above, namely lack of accounting for aneuploidy in cancer cells and inability to use an antibody to a protein with no known function or specific diagnostic use in view of the lack of reasonable expectation of copy number reflecting amount of expressed protein, it is maintained that it would require undue experimentation to use the claimed invention.

Applicants argue that the Examiner has named no particular reasons why the specification would not be enabling for how to use. The argument has been fully considered, but is not persuasive. As stated in the previous Office action on p. 5, lines 13-16, "The specification provides little beyond structural data and potential activities of the PRO339 polypeptide without guidance about which specific activities one could reasonable expect the polypeptide of encoding nucleic acid to possess as discussed above [under 35 USC 101]."

35 U.S.C. § 102

Claims 39-44 remain rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/63088 for the reasons set forth in the previous Office action (paper #11) on page 6, lines 5-10, and for the following reasons addressing the amendment to claim 44: WO 99/63088 teaches antibodies to PRO1281 (Figure 233), including bispecific antibodies wherein the antibody binds PRO1281 and an other antigen (p. 368, line 21- p. 370, line 13), that would for reasons of record be reasonably expected to bind the polypeptide of SEQ ID NO:339 of the instant application.

Applicants argue that WO 99/63088 cannot be an anticipatory reference because it does not disclose a protein with the sequence of PRO339 nor an antibody that specifically binds to SEQ ID NO:339 because according to the specification (p. 74, (cited as lines 34-35) lines 26-27), such an antibody cannot cross-react with other epitopes. The argument has been fully considered, but is not persuasive. First, the noted portion of the specification describes an epitope tagged polypeptide. An antibody to such a peptide would not cross-react with epitopes other than the epitope of the tagged polypeptide. This is distinct from an antibody that specifically binds a polypeptide that likely contains multiple epitopes. Nevertheless, for the epitope tagged polypeptide, it is stated (p. 74, lines 27-29) that, "Suitable tag polypeptides generally have at least six amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues)." WO 99/63088 has a region of 18 contiguous amino acids identical to SEQ ID NO:339 and multiple regions of at least 6 contiguous amino acids. These regions of identity are in addition to larger regions in which conservative amino acid substitutions are found within regions of identity. An antibody that specifically binds is generally understood by those of ordinary skill in the art to bind with specificity to the identified polypeptide, but may cross-react, binding to a lesser extent with other polypeptides. Absent evidence to the contrary and as stated (p. 6, lines 8-9) in the original rejection, [WO 99/63088 antibodies] "would be reasonably expected to bind the polypeptide with the sequence of SEQ ID NO:339 of the instant application because the proteins share large regions of high identity..."

35 U.S.C. § 103

Claims 39-44 remain rejected under 35 U.S.C. 103(a) as being unpatentable over GenBank Accession No. BAA92640 in view of Sibson et al. (WO 94/01548) and Godowski et al. (US Patent 6,030,831) for the reasons set forth in the previous Office action (paper #11) on pages 6-7 and for the following reasons addressing the amendment to claim 44: Godowski et al. also teach general methods of producing bivalent, also called bispecific, antibodies (col. 16, lines 24-29, and col. 18, lines 7-67) to secreted proteins, and also the use of antibodies in, for example, direct and indirect sandwich assays and immunopreciptation assays. It would have additionally been obvious to one of ordinary skill in the art to make an antibody, including a bivalent antibody, to the polypeptide of GenBank Accession No. BAA92640 because Sibson outlines the uses, advantages and general methods of making antibodies to proteins encoded by expressed nucleic acids and Godowski et al. teaches a variety of antibody types, including bivalent antibodies, and methods of making and using them.

Applicants argue that claims 50 and 51 (as appeared in the original rejection were not present in the instant application and it is unclear which pending claims, if any, the rejection is directed towards. The argument has been fully considered, but is not persuasive. The error was inadvertent and obvious. Since claims 50 and 51 do not exist in this application, and the same primary GenBank reference was used in both 35 USC 103 rejections, it is clear that both 103 rejections were over the 39-44 claims. Further, Applicants correctly interpreted the rejection and to what it corresponded.

Applicants argue GenBank Accession No. BAA92640 does not teach an antibody that binds a peptide. The argument has been fully considered, but is not persuasive. The rejection is one of obviousness instead of anticipation. In view of the prior art, an antibody that bound the encoded protein described by the GenBank would have been obvious.

Claims 39-44 remain rejected under 35 U.S.C. 103(a) as being unpatentable over GenBank Accession No. BAA92640 in view of Applicants' Admission on p. 34, lines 5-6 and Fleming et al. (Dev., 124:2973-81, 1997) and Godowski et al. (US Patent 6,030,831) for the reasons set forth in the previous Office action (paper #11) on pages 7-8 and for the following reasons addressing the amendment to claim 44. Godowski et al. also teach general methods of

producing bivalent, also called bispecific, antibodies (col. 16, lines 24-29, and col. 18, lines 7-67) to secreted proteins, and also the use of antibodies in, for example, direct and indirect sandwich assays and immunopreciptation assays. It would have additionally been obvious to one of ordinary skill in the art to make an antibody, including a bivalent antibody, to the polypeptide of GenBank Accession No. BAA92640 because Fleming et al. teach a secreted protein, fringe, which Applicants admits is structurally related to PRO339, and because Godowski et al. put the artisan of ordinary skill in possession of the necessary routine methods to and motivation for making bivalent antibodies, for example, to conduct sandwich assays and bind two different antigens for immunoprecipitation at the time the invention was made.

Applicants argue that for both 35 USC 103 rejections, the instant application receives an effective filing date of 2/11/2000 due to the utility supported by gene amplification data; therefore, GenBank Accession No. BAA92640 is not available as prior art. The argument has been fully considered, but is not persuasive. Because of the reasons discussed above for the rejections of 35 USC 101/112, 1st paragraph, the claimed invention lacks utility. It is maintained that effective filing date is 07/11/2001.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicants or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

April 24, 2003

CHRISTINE J. SAOUD
PRIMARY EXAMINER